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Micro-bubble Enhanced HIFU

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Abstract

High intensity focused ultrasound (HIFU) treatment that employs microbubbles to provide enhanced heating has been investigated in order to develop a less invasive and more rapid tumor ablation therapy. It has been demonstrated that microbubbles have significant effects on heating enhancement in vitro and in vivo experiments, however ultrasound propagation could be disturbed when there are too many microbubbles between the transducer and the focus. In this study, we develop a method to make a clear pass way for obtaining enhanced heating by using microbubbles just at the focus, thus avoiding heating on the pass way from the transducer to the target region. In this method, microbubbles are destroyed in front of the HIFU focus (on the transducer side) by irradiating a intense burst wave of microsecond order, before irradiating the ultrasound waves for heating the target region. The experiment is conducted in a medium of a polyacrylamide gel containing microbubbles, and a temperature-sensing liquid crystal sheet is set in the focus to observe the temperature distribution. The ultrasound frequency was 2.2 MHz and the intensity was 5000 W/cm2, and 20 burst waves were irradiated at pulse repetition frequency of 1 kHz. The number of wave pulses was varied. The continuous-wave frequency, intensity and irradiation time are 2.2 MHz, 1000 W/cm2 and 60 sec, respectively. As the number of pulses increased, the heating region moves from the transducer side to the focus. This is because microbubbles in front of the focus are destroyed and the ultrasound propagates around the target position effectively. These results suggest that the microbubble distribution and the heating position in the developed HIFU system can be controlled.

Keywords: Control of bubble distribution; HIFU; Micro-bubbles; Ultrasound contrast agent

1. Introduction

Medical ultrasound has attracted much attention due to its minimal invasiveness. Ultrasound imaging has been widely used as a method for real-time diagnosis. X-ray CT and MRI can generally visualize more minute structure,

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but the ultrasound imaging can clarify detail vascular structure when microbubbles are used as ultrasound contrast agents. The ultrasound contrast agents have been used for therapeutic purposes as well as diagnosis purposes. When the microbubbles are acoustically driven, they oscillate and emit acoustic pressure. At the same time, they convert some amount of the acoustic energy of the ultrasound to heat energy due to the dissipation and heat conduction.[1]-[2] Controlling actively the effect of the microbubbles, the novel therapeutic method has been investigated. For the therapeutic purpose, High Intensity Focused Ultrasound (HIFU) is applied. In HIFU therapy, the ultrasound is generated outside the body and focuses to the target tissue. The tissue is treated selectively and noninvasively with the highly concentrated energy in the tissue. HIFU has been used for many therapeutic applications. For example, tissue coagulation with the heat energy from the microbubbles [3]-[4], sonodynamic therapy [5], thrombolysis using acoustic emission from the microbubbles [6], gene transfer with the ultrasound and microbubbles [7]. HIFU lithotripsy (Cavitation Control Lithotripsy:CCL) using cavitation erosion [8]. However, previous studies by our group have revealed that ultrasound propagation is disturbed when there are microbubbles in front of the focus [9]-[10]. This means that it is difficult to occur the tissue coagulation at the focus. In addition, the destruction of encapsulated microbubbles has been reported [11]-[13]. So, we developed a method for destroying microbubbles on the transducer side by irradiating burst waves having durations of the order of microseconds with the goal of achieving accurate position control of heating in microbubble-enhanced HIFU. In this study, new methods for medical ultrasound with microbubbles are shown. One is the localized enhancement of heating for HIFU therapy using microbubble contrast agents, and the other is the analysis of the relationship between the microbubble distribution in a gel and the heating profile by varying the number of burst waves.

2. Heating effect of the micro-bubble in HIFU

HIFU (High Intensity Focused Ultrasound) have recently been applied in the treatment of cancer [14]-[16]. In the field of the bubble dynamics, it is known that the bubbles can play a role in converting mechanical energy into heat when they are subjected to an acoustic field. The effective use of the microbubbles can improve the HIFU treatment. In this section, the heating effect of the microbubbles is experimentally investigated in vitro and in vivo.

2.1. In vitro experiment

Figure 1 shows the experimental setup for in vitro experiments. The concave PZT ceramics diaphragms that have the natural frequencies of 2.2 MHz are used as the ultrasound transducer. The diameter of the transducer is 40 mm. The focal length is 40 mm. The polyacrylamide gel is put in the ultrasound field, and the gel has the cylindrical space whose depth is 10 mm and diameter is 10 mm. In the space, pure water and the liquid with Levovist® , one of the contrast agents, are injected. The bubble diameter is less than 10 μm and average is 1.3 μm. In order to measure the temperature distribution, a thermal liquid crystal sheet is used. The sheet has the temperature range from 40 to 45 degrees Celsius. The camera is set above the test section and the temperature distribution was taken.

Figure 2 shows the temperature rise around the focal region measured with a thermocouple. The ultrasound frequency is 2.2 MHz, the output power from the ultrasonic amplifier is 30 W, and the irradiation time is 60 sec. Figure 2 (a) shows the time history of the temperature rise and 2 (b) shows the change of the temperature rise in 60 s with changing the initial concentration of the microbubbles. From the results, the temperature rise increases with increasing the concentration of the microbubbles.

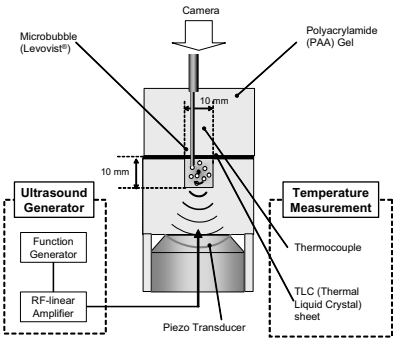

Fig.1 Experimental setup to measure the temperature rise in HIFU with microbubbles

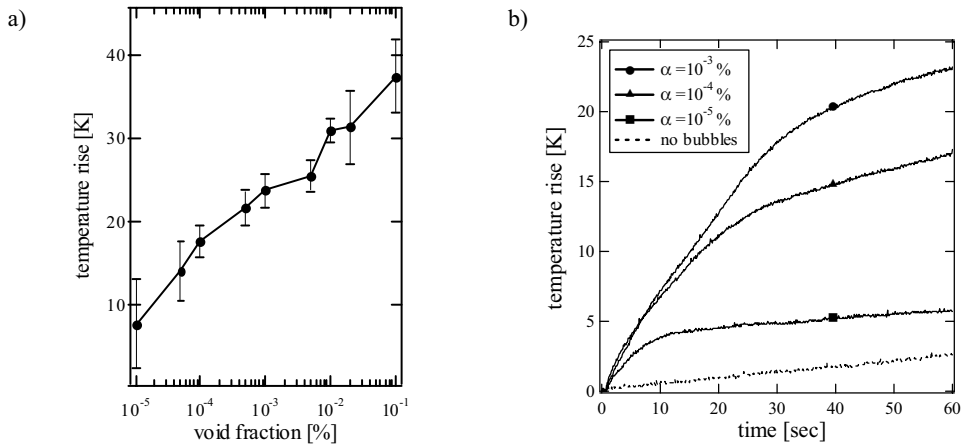

Fig.2 Temperature rise around the focal region. (a) Time history of the temperature rise, (b) Concentration of microbubbles and the temperature rise in 60 s

2.2. In vivo experiments

In the experiment, two rabbits were given Levovist® and other two rabbits were given normal saline as a control. Each rabbit was given one injection of 7 ml 300 mg/ml Levovist® or 7 ml saline intravenously. After 90 s of perfusion, the liver was exposed to HIFU for 60 s. The ultrasound frequency was 2.2 MHz and the output power from the ultrasonic amplifier is 10 W. A total of five or six HIFU exposures were performed within 10 min in each rabbit. In order to measure the temperature rise in the liver, four thermocouples were set several millimeters away from the focus of the ultrasound.

Figure 3 shows the time history of the temperature rise in the liver. Plotted data indicates a mean of 11 different HIFU areas in two rabbits in each group (Levovist® or saline). Hepatic temperature rose during HIFU in both groups, but it rose faster and to a higher level in the group that had received Levovist®. Figure 4 shows the volumes of the tissue coagulated by HIFU. The mean coagulated volume in the group that received Levovist® was

more than twice that in the group that received saline. It is confirmed that HIFU-induced lesions were larger in animals given Levovist® than in those given saline, and temperature increases 60 s after the start of exposure were also higher in the animals given Levovist® than in those given saline. The ease of clinical use of HIFU and its low cost will probably make it a very desirable treatment for some clinical conditions. Microbubble contrast agents, previously used for diagnostic purposes only, may also have a more direct role in therapeutic applications.

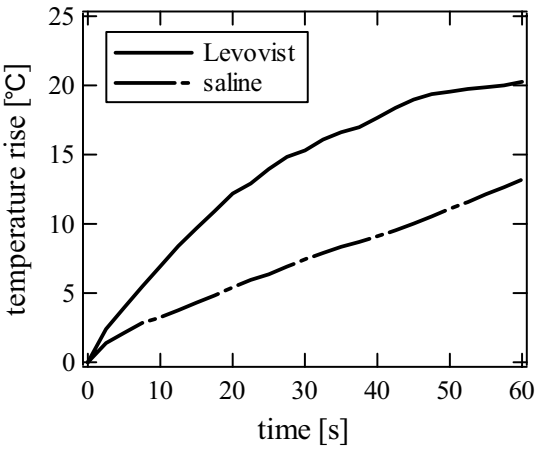

Fig.3 Temperature rise in the liver during HIFU exposure. Each point here indicates a mean of 11 different HIFU areas in two rabbits in each group (Levovist® or saline).

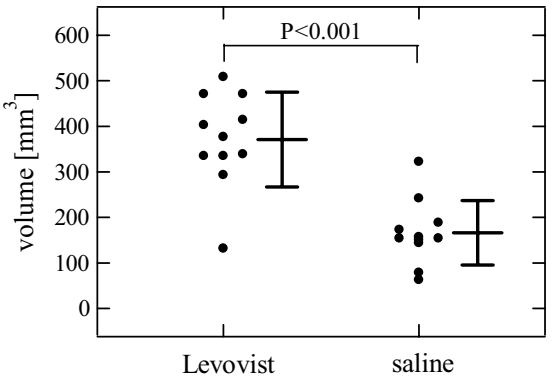

Fig.4 Volumes of the tissue coagulated by HIFU. The data shown are from 11 lesions in two rabbits in each group

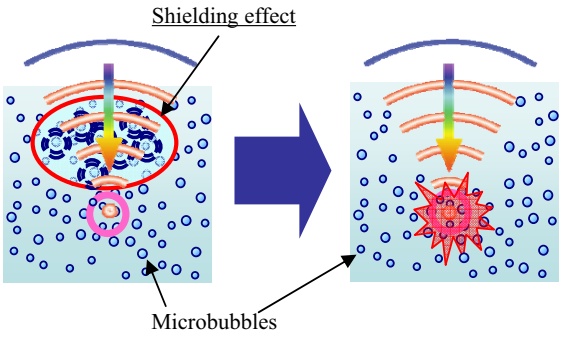

Fig.5 Idea to heat up the only focus. This method is that the very short burst wave destroys the microbubbles in front of focus that disturb the ultrasound propagation and make a path of ultrasound for heating.

2.3. Control of ablation region in microbubble enhanced HIFU

It is shown that microbubble constant agents could be a good heating enhanced role in HIFU treatment. On the other hand, it is reported that as concentration of microbubbles increase, heating position moves from the focus region to the transducer side [9]-[10]. This problem means that it is difficult to generate the heating location at the only focus in HIFU treatments using microbubbles. To solve this problem, we develop a new method for obtaining enhanced heating by using microbubbles just at the targeting region by avoiding unexpected heating in the transducer side. In this method, microbubbles are destroyed between the HIFU focus region and the transducer by irradiating intense burst wave shortly, before irradiating the ultrasound waves for heating the focal region. Fig.5 shows this idea. In this section, some experiments are conducted to evaluate the validity of this method.

2.4. Experimental method

Figure 6 shows the experimental setup. Figure 6(a) shows the setup for the temperature rise experiment. The piezoelectric transducer is 40 mm in diameter and its focal length is 40 mm. A container consisting of two sections separated by a PET film is filled with a polyacrylamide gel that contains microbubbles. The case is positioned such that its rear section lies in the HIFU focus. Two thermocouples are used to measure the temperatures in front of the focus (i.e., the transducer side of the focus) and two are used to measure the temperature at the focus. Figure 6(b) shows the setup for the temperature distribution experiment. The devices used to generate the ultrasound waves (i.e., the function generator, amplifier, etc.) are the same as those depicted in Fig. 1(a). The container (50 mm × 50 mm × 50 mm) is filled with a polyacrylamide gel containing microbubbles. A thermal liquid-crystal sheet, which changes color for temperatures in the range 50 to 60ºC, is positioned in the plane containing the ultrasound beam axis. A camera is used to record the color changes of this sheet.

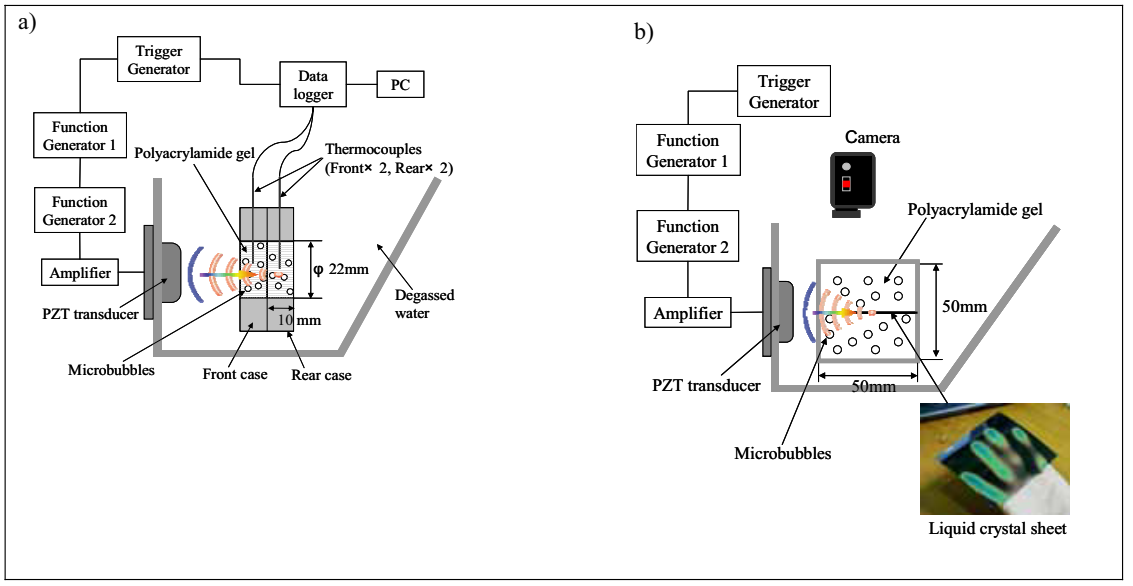

Fig.6 a) Experimental setup; (b) Temperature-distribution setup

Table 1. Ultrasound parameters for microbubble destruction

Frequency	2.2 [MHz]
Intensity	5000 [W/cm2]
Peak-to-peak pressure	29.7 [MPa]
No. of cycles	20
Pulse repetition freq. (PRF)	1 [kHz]
No. of pulses	0 - 10000

Table 2. Ultrasound parameters for heating

	Temperature rise	Temperature distribution
Frequency	2.2 [MHz]	
Intensity	1000	300 [W/cm2]
Peak-to-peak pressure	11.8	6.3 [MPa]
Exposure time	60 [s]	

Table 1 shows the ultrasound parameters for destroying microbubbles, and Table 2 shows the ultrasound parameters for heating. Figure 7 depicts the burst wave used to destroy microbubbles on the transducer side. In this experiment, we observe how the heating location shifts on varying the number of burst waves; the other burst wave parameters are kept constant. The microbubbles occupied a constant void fraction (10^{-5}). Levovist® microbubbles were used in this experiment.

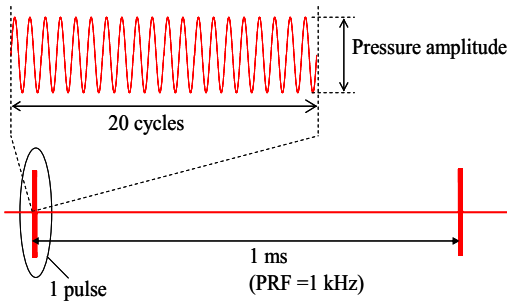

Fig.7 Burst wave used to destroy microbubbles on the transducer side

2.5. Results and discussion

First, the temperature rise as a function of time was measured three times by thermocouples for each number of pulses. Figure 8 shows the average temperature rise as a function of time at the focus for each number of pulses. The temperature rise increases as the number of pulses increases, except for 10000 pulses, which give only a slight temperature rise relative to the case of 0 pulses. The temperature rise is greatest when 100 pulses are used. This is because 100 pulses destroy most of the microbubbles in front of the focus enabling ultrasonic energy for heating to reach the focus. Next, Fig. 8 shows snapshots of the temperature distribution when each pulse is irradiated. In the case of no pulses, the microbubbles in front of the focus absorb ultrasonic energy resulting in heating in front of the focus, which is undesirable. As the number of pulses increases, the heating region moves towards the focus and increases in size. Compared to when there are no pulses, 100 pulses result in very good heating at the focus. This

shows that applying 100 pulses does not produce undesirable heating but does enable enhanced heating due to microbubbles.

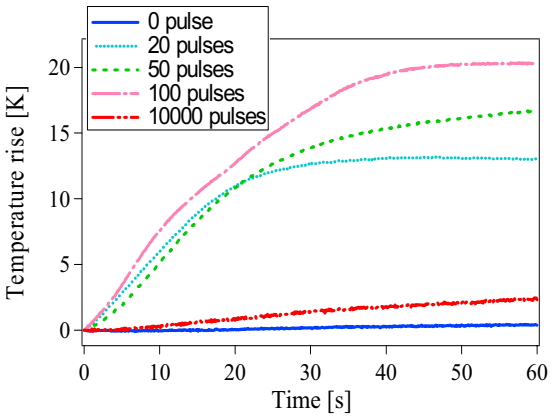

Fig. 8. Average temperature rise for different pulse numbers

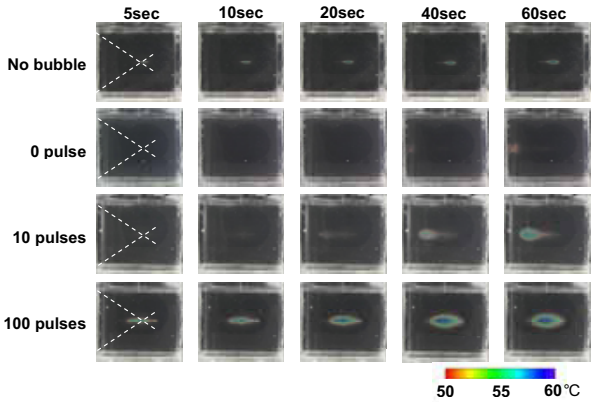

Fig.9 Snapshots of temperature distribution profile for different pulse numbers

Finally, we used a medical ultrasound scanner to examine the gels after ultrasound irradiation for microbubble destruction. Figure 10 shows ultrasound images for each burst pulse number. These results reveal that as the number of pulses increases more microbubbles are destroyed on the transducer side. Particularly in the case of 10 pulses, the heating region appears in front of the focus (Fig. 9). The reason for this may be that the microbubbles are not completely eliminated, and the remaining microbubbles cause heat generation. These results indicate that the degree of microbubble destruction depends on the number of pulses of very short, high-intensity ultrasound.

When a sufficient number of ultrasound pulses are applied to a gel containing microbubbles, most of the microbubbles are broken into smaller bubbles due to the fission by the violent collapse caused by the intense

ultrasound. Those tiny bubbles are not stabilized well by a surfactant or lipid so that the gas inside the bubble diffuses out from the bubble and the bubbles shrink quickly as illustrated in Fig.11.

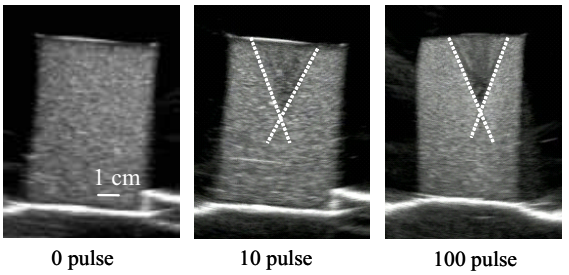

Fig.10 Ultrasound images of the gels after ultrasound irradiation showing the degree of bubble destruction for different pulse numbers.

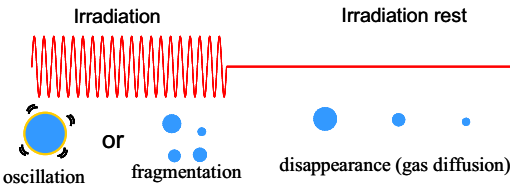

Fig.11 Bubble disappearance after the high intensity burst wave irradiation

Those fragmented bubbles cannot react as a contrast agent and also heat enhancer. However, the remaining nano-bubbles at the focal region can react to the high intensity ultrasound and the surrounding microbubbles also enhance the heat deposition, so that the targeting region is well treated as planed. The bubble response to the ultrasound of 2.2 MHz is shown in Fig.12. When the pressure amplitude is high enough, small bubbles, whose radii are less than 1 micro-meter, can oscillate violently to convert the pressure energy to heat. Thus, we can control the distribution of microbubbles in the gel, and allowing effective heating at the focus to be achieved. These results suggest that the microbubble distribution and the heating position in the HIFU treatment system can be well controlled.

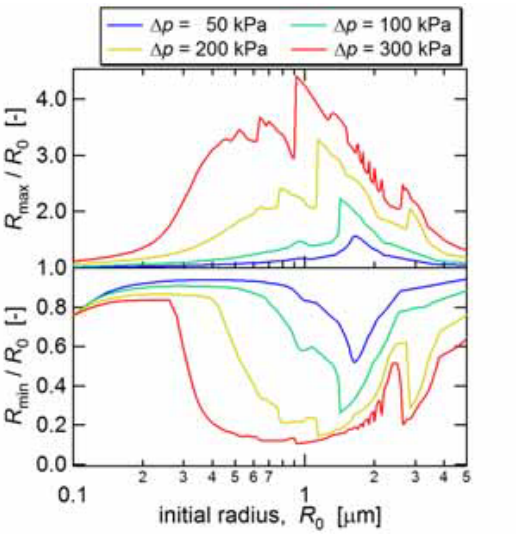

Fig.12 Bubble response in the ultrasound field

3. Conclusion

In the medical ultrasound field for both in diagnostic and therapeutic applications, microbubbles have recently been the subject of much interest. In this paper, firstly the heating effect of the microbubbles is experimentally investigated in vitro and in vivo. Secondly, to develop HFU treatment with microbubbles which the heating position is controlled accurately at the focus, the relationship between the microbubble distribution in a gel and the heating profile by varying the number of burst waves is experimentally investigated.

In both in vitro and in vivo experiments, microbubble constant agents enhance the heating effect in HIFU treatment. However, it is also important to investigate to control the coagulated region in the tissue, as the injection of the microbubbles makes it difficult to predict the distribution of the temperature rise correctly due to the large attenuation in the pass way to the focal region. In order to suppress heating in the pass way from the transducer to the focal region, intense burst waves for destroying microbubbles are irradiated into a gel phantom containing microbubbles and the temperature rise and distribution are investigated by varying the number of pulses consisting of the intense burst waves. The suggests by irradiating a sufficient number of burst waves and controlling the microbubble distribution in a gel phantom the microbubbles can be used to achieve heating at the focus. In the future, in order to realize microbubble-enhanced HIFU treatment, it is important to investigate the effectiveness of this method for different microbubbles contrast agent such as Sonazoid® and biological tissues in vivo.

Aknowledgements

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